PATENT SPECIFICATION

(11) 1391918

1391918

(21) Application No. 42163/72 (22) Filed 11 Sept. 1972
(31) Convention Application No. 2145282 (32) Filed 10 Sept. 1971 in
(33) Germany (DT)
(44) Complete Specification published 23 April 1975
(51) INT CL² C07C 91/30 A61K 29/02 C07C 101/04
(52) Index at acceptance
C2C 220 227 22Y 300 303 315 31Y 321 322 32Y 360 362 365 366 367 36Y 449 620 623 628 633 650 652 658 65X 662 669 798 79Y LF LR
A5B 760

(19) THE PATENT OFFICE LONDON

(54) IODOHYDROXPHENYL-AMINOALKANE DERIVATIVES AND PROCESS FOR THEIR MANUFACTURE

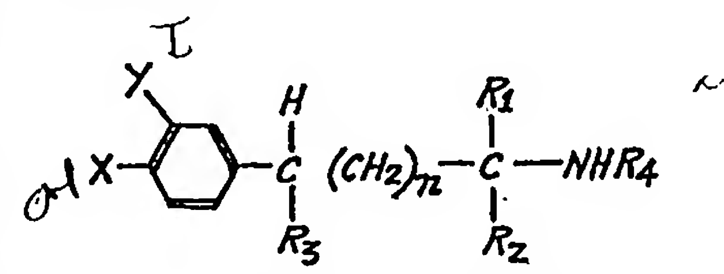
(71) We, HOECHST AKTIENGESELLSCHAFT, formerly known as Farbwerke Hoechst Aktiengesellschaft, vormals Meister Lucius & Brüning, a Body Corporate recognised under German Law, of 6230 Frankfurt/Main 80, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to iodohydroxyphenyl - aminoalkane derivatives and a method for their preparation.

Diagnosis of the function or the morphology of body organs and systems may be performed by administering radioactive compounds and then either examining blood samples or excreta for their activity content or measuring the activity content of organs by means of counting devices. For example, scintigraphy permits measurement of the area of radioactivity and thus an evaluation of the shape, size and morphological defects of organs. A prerequisite for this is that the target organs must contain a large amount of a test substance labelled with a gamma ray emitting nuclide. It is the object of the present invention to apply this technique to the diagnosis of tumours and the investigation of the adrenal glands. (Scintigraphy is a method of producing a two dimensional intensity-proportional picture of spatial distribution of a γ-ray emitting radionuclide by means of a radiation detection device).

It has been found that, after administration of ^{14}C-labelled α - methyl - β - dihydroxy - phenyl - alanine, a relatively large amount of ^{14}C is found in the adrenal medulla (cf. K. Patzschke et al., Zeitschrift für Naturforschung 1967, *22b*, pages 70 to 84). It has also been found that, among the biochemical intermediates in the biosynthesis of noradrenaline, dihydroxyphenyl-ethylamine when labelled with ^{14}C, affords the greatest enrichment of radioactivity in the adrenal medulla (cf. W. H. Beierwaltes et al., Journal of Nuclear Medicine 1967, *8*, pages 800 to 809). Owing to the short range of their radiation, however, beta particle emitting nuclides, for example, ^{14}C, are not suitable for measuring organs *in vivo*. It has, therefore, been necessary to prepare compounds labelled with gamma ray emitting nuclides which show a distribution pattern similar to that of the ^{14}C-labelled compounds. Previous attempts to use iodine 125 have failed, because nobody knew where to introduce the iodine into the dihydroxyphenyl-ethylamine derivatives without affecting their physiological properties.

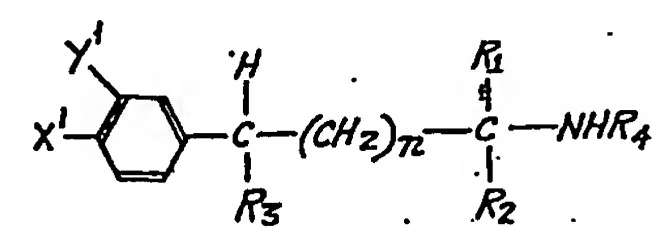
The present invention provides iodohydroxyphenyl-aminoalkane derivatives of the formula I



(I)

in which one of the substituents represented by X and Y is an iodine atom and the other is a hydroxyl group, R_1 represents a methyl group, R_2 represents a hydrogen atom or a carboxyl group, R_3 represents a hydrogen atom or a hydroxyl group, R_4 represents a hydrogen atom or a methyl group and n represents zero or the integer 1, the iodine atom being a radioactive nuclide, preferably iodine-123, iodine-125 or iodine-131.

The invention also provides a process for the manufacture of a compound of the general formula I, which comprises reacting a compound of the formula II



(II)

in which one of the substituents represented

[Price 33p]

6 - 11

by X' and Y' is a hydrogen atom and the other is a hydroxyl group, R_1, R_2 R_3 and R_4 and n are as defined above, with an iodinating agent comprising a radioactive isotope of iodine, or with an iodinating agent comprising a non-radioactive isotope of iodine and then replacing the non-radioactive iodine atom in the resulting compound by a radioactive iodine atom by means of an exchange reaction.

radioiodination

Suitable agents for iodination are preferably elementary iodine, iodine chloride or iodides, for example, sodium iodide or potassium iodide, the iodides being used in the presence of an iodizing agent, for example, an iodate, a peroxy-disulphate, hydrogen peroxide or chloramine T.

The reaction components may be used in stoichiometric amounts. It is, however, advantageous to use the compound of formula II in an at least 4-molar excess. Optimum yields are obtained, calculated on the iodine or iodide used, if the compound of formula II is present in a 10- or 20-molar excess. Any non-iodinated compounds of formula II remaining after the reaction are recovered during the working-up of the reaction mixture.

1m. 27 exces

The calculated amount of iodine may be used as elementary iodine, as iodide or as iodine chloride in an aqueous or alcoholic solution. When using carrier free radioactive iodine or in large batches where the activity exceeds 2 mCi, it is preferable to employ an aqueous iodide solution.

When elementary iodine is used, it is also advantageous to add one of the above oxidizing agents.

The reaction medium may be aqueous, aqueous-alcoholic or alcoholic. As alcohols there may be mentioned methanol, ethanol, propanol or butanol. Since alcohols are suitable only to a limited extent for administration to animals or human beings, aqueous systems are preferred for the synthesis and purification of the compounds of the invention.

The temperature of the iodination reaction may range from 0° to 90°C, preferably from 0° to 25°C, since the reaction then proceeds at a sufficiently high rate, so that formation of by-products is prevented and hardly any radioactive iodine escapes.

Iodination may be performed with a pH-range of from 0 to 9. Within the acid range the iodination reaction is slower, but at high pH-values the formation of by-products, especially of diiodo compounds, is promoted and re-oxidation of the iodide formed in the reaction is retarded. It is therefore preferable to choose a pH-value ranging from 1 to 5.

The compounds of the invention may be isolated and purified, in the case of large amounts, by precipitation in a neutral medium and recrystallization.

In the case of high specific activities and amounts of substance less than 1 mg, it is preferable to use chromatographic methods, for example, column chromatography, thin layer chromatography or paper chromatography.

For separation by column chromatography, a molecular sieve may be used, for example, a Sephadex-dextran or an ion exchanger, for example, an Amberlite cation exchanger. ("Sephadex" and "Amberlite" are Trade Marks). As eluent, an aqueous solution of a pH from 0 to 6 may be used, for example, a solution of hydrochloric acid, acetic acid, sodium acetate buffer or citrate buffer. In addition, an aqueous-alcoholic system, for example, methanol-water-hydrochloric acid, or an alcoholic system, for example, methanol-hydrochloric acid, may also be employed. Basic eluents are less suitable since they easily decompose the products of the invention.

Very small amounts are advantageously separated by means of paper chromatography, for example, using a system of methanol-2N acetic acid as the moving phase with subsequent elution with a dilute acid or a low-molecular-weight alcohol of strips cut from the paper.

According to this process, large amounts of the compounds of formula I can be prepared using inactive iodine and purified by column chromatography using one of the above eluents. If a volatile eluent is used, the crystallized compounds are obtained after removing the solvent.

For exchanging non-radioactive iodine, an at most 10^{-1}-molar, advantageously at from 10^{-2} to 10^{-4}-molar solution, generally an acid aqueous or alcoholic solution, of a compound of formula I containing non-radioactive iodine is prepared. To this solution, carrier free or non-carrier free radioactive iodide, preferably sodium iodide or potassium iodide, is added and the solution is heated while stirring to a temperature of from 50° to 90°C. The exchange is followed by paper electrophoresis on samples of the reaction mixture to determine the distribution of the radioactive iodine between the product of the invention and the iodide. After at least 90% of the iodide used has been exchanged, the solution is cooled, and the product of the invention is purified from the remaining iodide by precipitation or by chromatography as indicated above.

less than 5%

The compounds of the invention, labelled with radioactive iodine, are concentrated in the chromaffin tissue of the adrenals (adrenal medulla, pheochromocytomae) and of neuromae (neuroblastomae, ganglioneuromae) and permit a scintigram to be taken of these tissues. Moreover, the compounds of the invention are also concentrated in melanomae and are therefore suitable for their diagnosis.

Those compounds of the invention in which

the substituent R_3 is a hydroxyl group have an especially high affinity for the adrenal medulla. 24 Hours after injection of about 30 μCi of such a compound per animal the highest activity per gram was found in the adrenal glands of mice (NMRJ strain) and Wistar rats. It was up to fifty times higher than that in the liver, the organ showing the second-highest concentration of the compound.

By means of autoradiography of sagittal sections of whole animals it was confirmed that enrichment took place mainly in the adrenal medulla.

Thus, it is for the first time possible to visualize the adrenal medulla and other chromaffin tissues, which is of use for diagnostic purposes.

Tests for a melanoma diagnosis were performed on mice, in which melanotic melanoma (Harding Passey melanoma) was implanted under the skin of the neck. Groups of animals were killed at different times after intravenous injection of a compound of formula I and the radioactivity concentration of various organs was measured. It was found that those compounds in which the substituent R_3 is a hydrogen atom are concentrated in melanomae.

A favourable moment for examination was found to be about 24 hours after injection since then the activity of other organs was very low, especially that of the liver (near to or below 0.05% of the administered activity per gram), whilst it was about 1 to 2% per gram in the melanomae.

Thus, it is now possible to make an early diagnosis of melanomae and metastases thereof.

The present invention also provides a pharmaceutical preparation comprising a compound of the invention in admixture or conjunction with a pharmaceutically suitable carrier. The preparation is preferably in a form suitable for administration by injection, being for example, a physiological salt solution, preferably a physiological sodium chloride solution. Sterilization of the preparation is preferably carried out by sterile-filtration.

The following Examples illustrate the invention.

Example 1

The following solutions were prepared:

(a) 0.5 mg of KI in 0.25 ml of 0.1N HCl
(b) 0.5 mg of KIO_3 in 0.25 ml of 0.1N HCl
(c) 8 mg of α-methyl-tyrosine in 2 ml of 0.1N HCl and
(d) 6 mCi of $Na^{131}I$ in 0.1 ml of H_2O.

Solutions (a), (c) and (b) were successively added to solution (d); after 1 hour the mixture was placed on a Sephadex LH 20 column having a diameter of 9 mm and a height of 250 mm, and eluted with about 120 ml of 0.15-molar hydrochloric acid. UV-absorption and radioactivity of the eluate were measured continuously. The eluate was automatically collected in fractions of about 5 ml each. Successively, α-methyl-tyrosine, 3' - iodo - α - methyl - tyrosine and 3',5' - diiodo - α - methyl - tyrosine were eluted. The pH of the fractions containing the mono-iodo compound was adjusted to a physiological value by means of 4N NaOH. The solution thus prepared, optionally after sterilization by filtration was suitable for administration by injection.

Example 2.

The following solutions were prepared:

(a) 15 mg of 1 - (p - hydroxyphenyl) - 2 - aminopropane hydrobromide in 1.5 ml of water
(b) 1 mg of KIO_3 in 0.25 ml of HCl and
(c) 1 mg of KI containing 5 mCi of ^{131}I in 0.25 ml of 2N HCl.

Solutions (a) and (b) were successively added to solution (c); after 1 hour, the mixture was placed on a Sephadex LH 20 column (15×250 mm) and eluted with about 250 ml of a 0.05-molar citrate buffer of pH 3.5. The yield was 90% of the theoretical of 1 - (3' - iodo - 4' - hydroxy - phenyl) - 2 - aminopropane, calculated on radioactive iodide used.

In this manner, all the compounds of formula I can be obtained, especially those in which the substituent R_2 is a hydrogen atom.

Example 3

The following solutions were prepared:

(a) 15 mg of α-methyl-tyrosine in 2 ml of 2N ammonia
(b) 1 mg of KIO_3 in 0.25 ml of 2N HCl and
(c) 1 mg of KI containing 2 mCi of ^{131}I in 0.25 ml of 2N HCl.

Solution (b) and (a) were added to solution (c). After 1 hour, the pH was adjusted to a value between 1 and 0 by means of 1N hydrochloric acid, the mixture was placed on a Sephadex LH20 column having a diameter of 15 mm and a height of 900 mm, and eluted with about 200 ml of water. 85 to 90% of the theoretical amount of 3' - iodo - α - methyl - tyrosine were obtained, calculated on radioactive iodide used.

In this manner, all the compounds of formula I can be prepared, especially those in which the substituent R_2 is a carboxyl group.

Example 4

15 mg of α-methyl-tyrosine were dissolved in 2 ml of 4N ammonia; to this solution, an aqueous solution of 1 mg of potassium iodide with 1 mCi of $Na^{131}I$ and a freshly prepared solution of 5 mg of chloramine T in 2 ml of water was added. After 1 hour, the mixture was neutralized by means of 1N hydrochloric acid and purified by chromatography as described in any one of Examples 1 to 3. 80 to

85% of the theoretical yield of 3′ - iodo - α - methyl - tyrosine were obtained.

Example 5

The following solutions were prepared:

(a) 20 mg of α-methyl-tyrosine in 0.5 ml of 1N HCl and

(b) 500 μCi of ^{131}I in 0.23 ml of an iodine chloride solution (5.7 mg of I per ml).

Solution (b) was added dropwise to solution (a), the pH was adjusted to 4—5 by means of 1N NaOH and the precipitate was separated from the supernatant by centrifugation. The supernatant contained 3′ - iodo - α - methyl - tyrosine, the purity of which was examined by paper chromatography.

Example 6

100 mg of α-methyl-tyrosine were dissolved in 6 ml of 0.1N hydrochloric acid and the solution was combined with a solution of 20 mg of KIO_3 in 2 ml of 0.1N HCl. To this solution, a solution of 20 mg of KI in 2 ml of 0.1N HCl was slowly added. After 1 hour, the mixture was placed on a Sephadex LH 20 column having a diameter of 25 mm and a height of 400 mm, and eluted with 0.1% acetic acid. Successively, α-methyl-tyrosine, 3′ - iodo - α - methyl - tyrosine and a small amount of 3′,5′ - diiodo - α - methyl - tyrosine were eluted. By evaporation of the corresponding fractions, 3′ - iodo - α - methyl - tyrosine were obtained in a yield of 70% of the theoretical, calculated on iodide and iodate.

In this manner, the following compounds were prepared:

3′ - Iodo - α - methyl - tyrosine, melting point 250°C (decomposition),

4′ - iodo - α - methyl - m - tyrosine, m.p. 223°C (decomposition) and

4 - (3′ - iodo - 4′ - hydroxyphenyl) - 2 - amino - 2 - carboxy - butane, m.p. 239°C (decomposition).

From any one of the above compounds a solution of 0.1 to 3 mg per ml in 0.1% acetic acid or in an aqueous buffer solution of pH 4.0 was prepared. To this solution, 0.1 to 1 mCi of carrier free Na^{131}I was added. The solution was heated at 60—70°C until at least 90% of the radioactive iodide used were present in an organic linkage. The radioactive product of the invention could be purified by precipitation or by chromatography as described in any one of the above Examples.

Example 7

A solution of 100 mg of 1 - (4′ - hydroxyphenyl) - 1 - hydroxy - 2 - methylamino - propane and 20 mg of potassium iodide in 8 ml of 0.1N HCl was cooled to 10°C and a solution of 20 mg of KIO_3 in 2 ml of water was added dropwise thereto. At room temperature, the solution was stirred until 1 ml of a starch solution no longer turned a blue colour when a drop of the reaction solution was added (about 1 hour). The mixture was then placed on a Sephadex LH 20 column (25×400 mm) and eluted with a citrate buffer of pH 3.4. The fractions containing 1 - (3′ - iodo - 4′ - hydroxyphenyl) - 1 - hydroxy - 2 - methylamino - propane were concentrated to a volume of about 5 ml under reduced pressure. To remove salts this solution was placed on a Sephadex LH 20 column (15×900 mm) and eluted with 0.1% acetic acid. The fractions of 1 - (3′ - iodo - 4′ - hydroxy - phenyl) - 1 - hydroxy - 2 - methylamino - propane were collected and evaporated to dryness. The residue crystallized at reduced pressure in a desiccator after some days. The yield was 50—60% of the theoretical, calculated on iodide and iodate.

The purity of the product of the invention could be checked by paper chromatography in a system of butanol-2N acetic acid (moving phase). After a development time of 15 hours, the product was made visible by spraying the chromatograph with a solution of diazotized sulphanilic acid.

In this manner, the following compounds were prepared:

1 - (3′ - iodo - 4′ - hydroxyphenyl) - 2 - amino - propane

1 - (3′ - hydroxy - 4′ - iodophenyl) - 2 - amino - propane

1 - (3′ - iodo - 4′ - hydroxyphenyl) - 1 - hydroxy - 2 - amino - propane

1 - (3′ - hydroxy - 4′ - iodophenyl) - 1 - hydroxy - 2 - amino - propane

1 - (3′ - iodo - 4′ - hydroxyphenyl) - 2 - methylamino - propane

According to this process, all the products of formula I can be prepared containing non-radioactive iodine, especially those which contain no carboxyl group.

Non-radioactive iodine in these compounds was exchanged, preferably with radioactive carrier free iodine as disclosed in the second part of Example 6.

Example 8

The following solutions were prepared:

(a) 1 g of 1 - (4′ - hydroxyphenyl) - 1 - hydroxy - 2 - amino - propane hydrochloride and 0.2 g of KIO_3 in 20 ml of water and

(b) 0.2 g of KI in 5 ml of 1N HCl.

Solution (b) was slowly added dropwise while stirring at room temperature to solution (a). When the mixture contained no more free iodine, it was placed on a Sephadex LH 20 column (2.5×100 cm) and eluted with a total amount of 500 ml f 0.05-molar NaH_2PO_4-solution. While continuously checking the UV-absorption of the eluate, the starting material, the monoiod compound thereof and the diiodo compound thereof were eluted

successively in fractions of about 5 ml each.

The fractions of the monoiodo compound of three such runs were combined, concentrated under reduced pressure to a volume of about 20 ml, placed on a Sephadex G 25 column (5×100 cm) and eluted with a total amount of 4 litres of 0.1N acetic acid. The fractions of 1 - (3′ - iodo - 4′ - hydroxyphenyl) - 1 - hydroxy - 2 - amino - propane were collected, concentrated to dryness, dissolved in 10 ml of 1N hydrochloric acid, again concentrated to dryness, dissolved in 10 ml of 0.1N hydrochloric acid and precipitated with acetone. The crystallized precipitate was suction-filtered, washed with acetone and ether and dried in a desiccator under reduced pressure.

The yield was 75—80% of the theoretical, calculated on iodide and iodate used. Non-radioactive iodine in these compounds was exchanged, preferably with radioactive carrier free iodine as disclosed in the second part of Example 6.

Example 9

For examining the concentration of the products of the invention in organs, 36 male white Wistar rats were injected each with about 30 μCi of 1 - (3′ - iodo - 4′ - hydroxyphenyl) - 1 - hydroxy - 2 - amino - propane - ^{131}I. The dose administered was determined accurately for each individual animal.

After periods of time indicated in the following Table, 6 animals were killed, the appropriate organs were taken out and weighed, and the content of radioactive iodine therein was determined.

Radioactivity was calculated in percentage per gram of organ, the dose administered being 100%. The following Table shows the average value of radioactivity obtained from the results on 6 animals.

TABLE

Organ	Period after administration in hours 1	6	12	18	24	30
Liver	2.98	0.18	0.018	0.009	0.007	0.004
Adrenal gland	0.95	0.72	0.46	0.30	0.28	0.18
Muscles	0.16	0.01	0.002	0.001	0.001	0.0004
Blood	0.17	0.026	0.009	0.005	0.004	0.002
Ratio of liver: adrenal gland	3:1	1:4	1:25	1:33	1:40	1:45

Example 10

The concentration of 3′ - iodo - α - methyl - tyrosine - ^{131}I in melanomae was examined on white mice (NMRJ), in which a Harding-Passey melanoma was implanted under their neck skins. 24 Animals were injected each with about 30 μCi of the compound in the tail vein. The dose administered was determined accurately for each individual animal. After the periods of time indicated in the following Table, 6 animals were killed, the appropriate organs and tissues were taken out and weighed, and the content of radioactive iodine therein was determined.

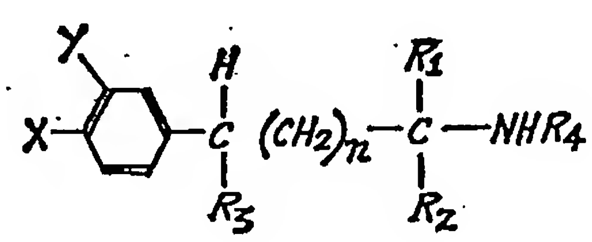
Radioactivity was calculated per gram of organ and indicated in per cent of the dose administered in the following Table. Each value given in the Table is the average value obtained from 6 animals.

TABLE

Organ	Period after administration in hours 12	18	24	30
Liver	0.13	0.013	0.015	0.01
Tumour	2.53	1.09	1.36	0.96
Muscles	0.07	0.003	0.007	0.003
Blood	0.21	0.01	0.018	0.02
Ratio of liver: tumour	1:20	1:80	1:90	1:95

WHAT WE CLAIM IS:—

1. An iodohydroxyphenyl-aminoalkane derivative of the formula I



(I)

in which one of the substituents represented by X and Y is an iodine atom and the other is a hydroxyl group, R_1 represents a methyl group, R_2 represents a hydrogen atom or a carboxyl group, R_3 represents a hydrogen atom or a hydroxyl group, R_4 represents a hydrogen atom or a methyl group and n represents zero or the integer 1, the iodine atom being a radioactive nuclide.

2. A compound as claimed in claim 1, wherein the radioactive iodine in iodine-123, iodine-125 or iodine-131.

3. 3′ - ^{131}iodo - α - methyl - tyrosine.

4. 4′ - ^{131}iodo - α - methyl - *m* - tyrosine.

5. 4 - (3′ - ^{131}iodo - 4′ - hydroxyphenyl) - 2 - amino - 2 - carboxy - butane.

6. 1 - (3′ - ^{131}iod - 4′ - hydroxyphenyl) - 2 - amino - propane.

7. 1 - (3′ - hydroxy - 4′ - ^{131}iodophenyl) - 2 - amino propane.

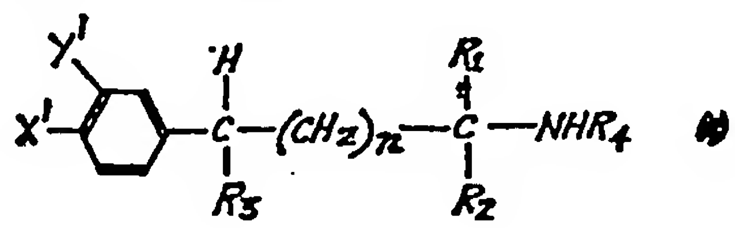
8. 1 - (3′ - ^{131}iodo - 4′ - hydroxyphenyl) - 1 - hydroxy - 2 - amino - propane.

9. 1 - (3′ - hydroxy - 4′ - ^{131}iodophenyl) - 1 - hydroxy - 2 - amino - propane.

10. 1 - (3′ - ^{131}iodo - 4′ - hydroxyphenyl) - 1 - hydroxy - 2 - methylamino - propane.

11. 1 - (3′ - ^{131}iodo - 4′ - hydroxyphenyl) - 2 - methylamino - propane.

12. A process for the manufacture of a compound of the general formula I as claimed in claim 1 which comprises reacting a compound of the formula II



in which one of the substituents represented by X′ and Y′ is a hydrogen atom and the other is a hydroxyl group and R_1 to R_4 and n have the meanings given in Claim 1, with an iodinating agent comprising a radioactive isotope of iodine, or with an iodinating agent comprising a non-radioactive isotope of iodine and then replacing the non-radioactive iodine atom in the resulting compound by a radioactive iodine atom by means of an exchange reaction.

13. A process as claimed in claim 12, wherein the iodinating agent is elementary iodine, iodine chloride or an iodide.

14. A process as claimed in claim 13, wherein an oxidising agent is present when elementary iodine or an iodide is used.

15. A process as claimed in claim 14, wherein the oxidising agent is an iodate, a peroxy-di-sulphate, hydrogen peroxide or chloramine T.

16. A process as claimed in any one of claims 12 to 15, wherein the radioactive isotope of iodine is iodine-123, iodine-125 or iodine-131.

17. A process as claimed in any one of claims 12 to 16, wherein the compounds of formula II is used in at least 4-molar excess relative to the iodinating agent.

18. A process as claimed in claim 17, wherein the compound of formula II is present in a from 10- to 20-molar excess.

19. A process as claimed in any one of claims 12 to 18, wherein when a carrier-free radioactive isotope is used, or when the activity exceeds 2 mCi, an aqueous iodide solution is used as the iodinating agent.

20. A process as claimed in any one of claims 12 to 19, wherein the temperature of the iodination reaction is within the range of from 0° to 90°C.

21. A process as claimed in claim 20, wherein the temperature is within the range of from 0° to 25°C.

22. A process as claimed in any one of claims 12 to 21, wherein the pH-value of the iodination reaction is within the range of from 1 to 5.

23. A process as claimed in any one of claims 12 to 22, wherein the resulting compound, wherein the iodine atom is radioactive or non-radioactive, is isolated and purified.

24. A process as claimed in any one of claims 12 to 23, wherein a non-radioactive iodine atom in the resulting compound is exchanged by reaction with a carrier free or non-carrier free radioactive iodide.

25. A process as claimed in claim 24, wherein the resulting compound is present in solution in a concentration of at most 10^{-1} molar.

26. A process as claimed in claim 25, wherein the solution is from 10^{-2} to 10^{-4} molar.

27. A process as claimed in any one of claims 24 to 26, wherein the reaction temperature is from 50° to 90°C.

28. A process as claimed in claim 12, conducted substantially as described in any one of Examples 1 to 8 herein.

29. A compound as claimed in any one of claims 1 to 11, whenever produced by a process as claimed in claim 12.

30. A pharmaceutical preparation which comprises a compound as claimed in any one of claims 1 to 11 or claim 29, in admixture or conjunction with a pharmaceutically suitable carrier.

31. A pharmaceutical preparation as claimed in claim 30, in a form suitable for administration by injection.

32. A pharmaceutical preparation as claimed in claim 30 or claim 31, in the form of a physiological salt solution of the compound as claimed in any one of claims 1 to 11 or claim 29.

ABEL & IMRAY
Chartered Patent Agents,
Northumberland House,
303—306 High Holborn,
London WC1V 7LH.

Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1975.
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.